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Concomitant statin use does not impair the clinical outcome of patients with diffuse large B cell lymphoma treated with rituximab-CHOP

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ORIGINAL ARTICLE

Concomitant statin use does not impair the clinical outcome of patients with diffuse large B cell lymphoma treated with rituximab-CHOP

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Abstract Preclinical data indicated a detrimental effect of statins on the anti-lymphoma activity of rituximab. We evaluated the impact of concomitant statin medication on the response and survival of patients with diffuse large B cell lymphoma (DLBCL) receiving rituximab–cyclophosphamide, doxorubicin, vincristine, prednisone (R-CHOP) as first-line therapy. Medical histories of patients with DLBCL who were treated with R-CHOP as first-line therapy were assessed for concomitant statin use, response after completion of chemotherapy, event-free survival (EFS), and overall survival (OS). Furthermore, 2-[^{18}F]fluor-2-deoxyglucose (FDG)-PET/CT results after completion of first-line therapy were compared between the groups. Overall, 145 patients with DLBCL treated with R-CHOP from January 2001 to December 2009 were analyzed. Twenty-one (15%) patients received statins throughout therapy. Five-year EFS was 67.3% in patients without statins compared with 79% in patients receiving statins during R-CHOP (HR, 0.47; 95% CI, 0.15–1.54, p=0.2). Five-year OS was 81.4% for patients without statins compared with 93.3% for patients taking statins (HR, 0.58; 95% CI 0.07–4.55, p=0.6). There were no statistically significant differences in the rates of complete remissions between the two groups (75% in the non-statin group versus 86% in the statin group, p=0.45). A trend toward a lower rate of complete metabolic responses in FDG-PET/CT after chemotherapy was seen in patients without statin medication compared with the patients taking statins (84% versus 92%, p=0.068). Concomitant statin use had no adverse impact on response to chemotherapy, EFS, and OS in patients treated with R-CHOP for DLBCL.

Keywords Statins · Diffuse large B cell lymphoma · Rituximab · R-CHOP · Survival

Abbreviations

DLBCL	Diffuse large B cell lymphoma
R-CHOP	Rituximab–cyclophosphamide, doxorubicin, vincristine, prednisone
EFS	Event-free survival
OS	Overall survival
FDG-PET	2-[^{18}F]fluor-2-deoxyglucose–positron emissions tomography
CT	Computed tomography
CD20	Cluster of differentiation 20
IPI	International prognostic index
HR	Hazard ratio
CI	Confidence interval
CR	Complete remission

Panagiotis Samaras and Helen Heider contributed equally to this work.

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uCR	Unconfirmed complete remission
PR	Partial remission
SD	Stable disease
PD	Progressive disease
HIV	Human immunodeficiency virus
HMG-CoAR	3-Hydroxy-3-methylgutaryl coenzyme A reductase
CDC	Complement-dependent cytotoxicity
ADCC	Antibody-dependent cellular cytotoxicity
mAb	Monoclonal antibody

Introduction

The prognosis of patients with aggressive non-Hodgkin's B cell lymphoma has been improved in the last decade by implementation of the monoclonal antibody (mAb) rituximab into standard first-line chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) [1, 2]. The therapeutic efficacy of rituximab is directed against the B cell surface phosphoprotein CD20 [3]. A recently published study reported that 3-hydroxy-3-methylgutaryl coenzyme A reductase (HMG-CoAR) inhibitors, so-called statins, are causing conformational changes of the CD20 epitope due to statin-induced cholesterol depletion, resulting in impaired binding of rituximab to CD20 and reduced complement-dependent cytotoxicity (CDC) and antibody-dependent cellular cytotoxicity (ADCC) in vitro. The authors concluded that intake of statins may reduce the antitumor activity of rituximab-containing chemotherapy in lymphoma patients [4]. This finding raised concerns on the efficacy of lymphoma treatment with rituximab in patients who are on concomitant statin medication for cardiovascular diseases. Some authors have even suggested that patients should discontinue statins before the onset of rituximab-containing chemotherapy [5, 6].

Recently, one study evaluating the impact of statins on the clinical outcome of lymphoma patients has been reported from a Japanese group. In this study, no adverse impact of statins on survival after R-CHOP treatment was seen [7]. While we were preparing the final manuscript, a second article has been published online. No differences in outcome regarding DLBCL were reported, but, surprisingly, patients with follicular lymphoma under statin medication had a better event-free survival (EFS) than patients not taking them [8]. To address this question, also in light of these two reports, we performed a retrospective analysis of the patient collective with diffuse large B cell lymphoma (DLBCL) treated with rituximab and CHOP at two institutions, University Hospital Zürich and Triemli City Hospital Zürich, during the last 8 years. Additionally, since the value of 2-[^{18}F] fluor-2-deoxyglucose–positron emissions tomography/computed tomography (FDG-PET/CT) has been shown for the response evaluation of DLBCL [9], we were also interested to see if differences in the metabolic response of the lymphoma tissue were present in patients taking statins compared to patients not using them.

Materials and methods

Records from patients with newly diagnosed DLBCL who received R-CHOP as first-line therapy at University Hospital Zürich or Triemli City Hospital Zürich were reviewed. Patients with initial low-grade lymphoma and secondary transformation to DLBCL were allowed for the analysis, as were patients with underlying HIV infection. Patients with primary central nervous system lymphoma or primary testicular lymphoma were excluded from the analysis. Data regarding lymphoma stage, international prognostic index (IPI), extranodal disease, response to treatment, EFS, and OS were collected. Duration and number of chemotherapy cycles were also documented. Patients receiving FDG-PET/CT imaging before and after completion of chemotherapy were analyzed for differences in the metabolic response of the lymphoma.

EFS was defined as time from first diagnosis of DLBCL to the time of first recurrence, as verified by histology, time to progression, as assessed by imaging during or after completion of first-line chemotherapy, or death. Overall survival (OS) was defined as time from initial diagnosis to the time of death by any cause, as documented in the patient charts.

The study was approved by our local ethics committee.

Statistics

Descriptive statistics (median and range, or counts) were calculated for all variables. Comparisons of group characteristics were performed using a Mann–Whitney *U* test (continuous data) or Fisher's exact test (categorical). Event-free and overall survival were calculated from the date of diagnosis and censored at the date of last follow-up. Survival curves were computed using the method of Kaplan and Meier and compared using the log-rank test [10, 11]. Values of $p<0.05$ were considered statistically significant. All analyses were performed in the R programming language [12].

Results

Between January 2001 and December 2009, a total of 145 patients received R-CHOP as first-line chemotherapy for

DLBCL. De novo DLBCL was diagnosed in 135 (93%) patients, while transformation from indolent lymphoma occurred in ten (7%) patients. Out of the entire patient population, 21 (15%) patients were on statin medication at the time of chemotherapy. The statins used were atorvastatin (n=9, 43%; mean daily dose 28±24 mg), simvastatin (n=7, 33.5%; mean daily dose 31±11 mg), pravastatin (n=4, 19%; mean daily dose 30±12 mg), and fluvastatin (n=1, 4.5%; daily dose 80 mg). No significant differences in terms of gender, lymphoma stage, or IPI score were seen between the two groups, but patients taking statins were significantly older than patients without statin intake (median 63.2 versus 56.3 years, p=0.0033; Table 1).

The median observed follow-up time for all patients was 24.4 months (range, 2.27–98 months). The entire patient population had an EFS of 69% (95% confidence interval (CI), 60.7–78.5%) at 5 years and an OS of 82.6% (95% CI, 70.8–96.3%) at 5 years. The median EFS and OS were not reached during follow-up. EFS was 67.3% at 5 years for the patient subgroup without statins compared with 79% for patients who had received statins during R-CHOP treatment (hazard ratio (HR), 0.47; 95% CI, 0.15–1.54, p=0.2; Fig. 1). In addition, there was no significant difference in OS at 5 years, with 81.4% still alive in the patient subgroup without statins compared with 93.3% for patients who had received them during R-CHOP treatment (HR, 0.58; 95% CI, 0.07–4.55, p=0.6; Fig. 2).

The rate of complete remissions or unconfirmed complete remissions after treatment with R-CHOP was 75% for the patient subgroup without statins compared with 86% for patients receiving statins (p=0.45). A subset of 69 (48%) patients had been analyzed by FDG-PET/CT before and after completion of chemotherapy for response assessment, 57 (83%) patients in the non-statin group, and 12 (17%) patients in the statin group. In the non-statin group, 84% of patients had a documented complete metabolic response after R-CHOP compared with 92% in the statin group (p=0.068; Table 2).

Table 1 Patient characteristics

Parameter	Statin use (n=21)	No statin use (n=124)	p value
Age			
≤60 years—no. (%)	8 (38)	78 (63)	
>60 years—no. (%)	13 (62)	46 (37)	0.053
Median (years)	63.2	56.3	
Range (years)	45.3–87.5	15.5–85.5	0.0033
Gender			
Male—no. (%)	16 (76)	66 (53)	
Female—no. (%)	5 (24)	58 (47)	0.059
Lymphoma stage			
Early (1/2)—no. (%)	16 (76)	65 (52)	
Advanced (3/4)—no. (%)	5 (24)	59 (48)	0.057
IPI score			
0–1—no. (%)	11 (53)	64 (53)	
2–3—no. (%)	7 (33)	48 (40)	
≥4—no. (%)	3 (14)	9 (7)	0.52
Extranodal disease			
Yes—no. (%)	15 (71)	81 (66)	
No—no. (%)	6 (29)	42 (34)	0.8
DLBCL			
De novo	19 (91)	116 (94)	
Secondary transformation	2 (9)	8 (6)	0.64
HIV-associated lymphoma			
Yes—no. (%)	1 (5)	10 (8)	
No—no. (%)	20 (95)	114 (92)	1.0
CHOP—number of cycles			
Median	6	6	
Range	3–6	2–8	0.12
Rituximab—number of cycles			
Median	6	6	
Range	3–8	2–8	0.71

Discussion

In the present study, we did not find any statistically significant adverse impact of statin medication on the

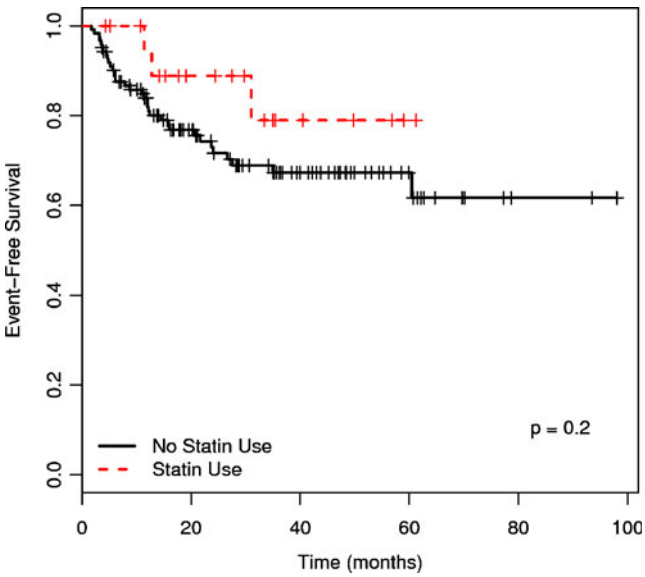

Fig. 1 Kaplan–Meier analysis of the event-free survival (*EFS*) of patients without statin use compared with patients receiving statin medication during R-CHOP treatment. EFS at 5 years was 67.3% in patients without statins compared with 79% in patients who had received them during treatment (HR, 0.47; 95% CI, 0.15–1.54, p=0.2). Median EFS was not reached in both groups. *Dashed line* patients with statins; *solid line* patients without statins

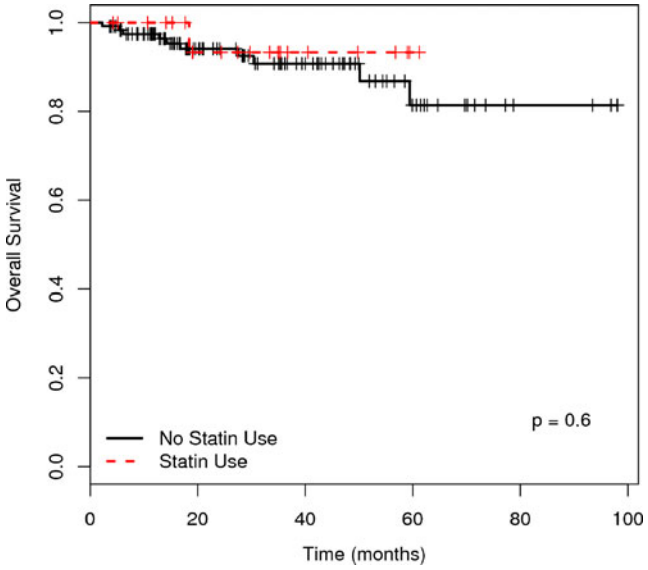

Fig. 2 Kaplan–Meier analysis of the overall survival (*OS*) of patients without statin use compared with the patients receiving statin medication during R-CHOP treatment. OS at 5 years was 81.4% in patients without statins compared with 93.3% in patients who received them during treatment (HR, 0.58; 95% CI, 0.07–4.55, p=0.6). Median OS was not reached in both groups. *Dashed line* patients with statins; *solid line* patients without statins

response and the survival of patients with DLBCL treated with R-CHOP first-line chemotherapy. On the contrary, we observed a trend toward an improved outcome in the subgroup of patients taking concomitant statins during chemotherapy. Patients taking statins showed a trend toward more complete metabolic responses in FDG-PET/CT after completion of chemotherapy than patients without statins (p=0.068). This result is even more remarkable when we take into account that our patients using statins were significantly older than the patients not taking them, as age is known to be a negative prognostic marker for lymphoma patients [13-16]. Our findings are in accordance with a recently published clinical trial evaluating the same question in a Japanese cohort. This study also showed a trend toward improved EFS and OS in patients being on statin medication during R-CHOP treatment without reaching statistical significance [7]. Finally, a second study reported recently also found no differences in outcome of DLBCL patients, but, interestingly, statin use was a positive prognostic factor in patients with follicular lymphoma irrespective of treatment [8].

How can the discrepancy between the in vitro observed changes of CD20 conformation on the surface of malignant B lymphocytes, which were linked to an impaired rituximab-mediated CDC and ADCC against lymphoma cells, and our and others' clinical data be explained? Though in vitro and in vivo correlations are often ambiguous, plasma levels achieved by common doses of statins used in the clinical routine are much lower than the concentrations used in the preclinical study. Maximum plasma concentrations of lovastatin, when given at therapeutic single daily doses of 20–80 mg, are reported to be in the range of 1.53–23.1 ng/ml [17-19]. In contrast, to achieve a significant abrogation of the anti-lymphoma effect of rituximab in vitro, lymphoma cells had to be incubated with lovastatin at concentrations of more than 2,000 ng/ml in vitro. Even the lowest lovastatin concentration tested (400 ng/ml) was not effective for a significant impairment of rituximab activity and is still substantially higher than the documented in vivo peak plasma levels [4]. The same applies to the other statins used such as atorvastatin. Plasma levels for atorvastatin ranging from 1.8 to 23 ng/ml have been reported in healthy or hypercholesterolemic individuals [20-23], but the concentration needed to show an adverse influence of statins on CDC was 275 to 2,750 times higher [4]. However, the authors observed a reduced binding of the anti-CD20 mAb ofatumumab to its target epitope in a small patient cohort treated with atorvastatin 80 mg daily. Taking the available clinical data and the aforementioned methodological details of the in vitro study into account, we hypothesize that a reduction of rituximab binding to CD20 does not necessarily translate into a reduced anti-lymphoma activity. On the other hand, additional anti-lymphoma effects of statins may also be, in part, responsible for the trend toward improved outcome of patients with statin treatment [24-26].

The main limitation of our study is the small patient number, especially for patients treated with statins. A post hoc power analysis indicated that the power for the log-rank test for event-free survival was approximately 35%.

Table 2 Remission rates and PET response

Response after chemotherapy	Statin use (n=21)	No statin use (n=124)	p value
CR/uCR—no. (%)	18 (86)	93 (75)	
PR—no. (%)	3 (14)	19 (15)	
SD/PD—no. (%)	0 (0)	12 (10)	0.45
Metabolic activity in post-treatment PET	Statin use (n=12)	No statin use (n=57)	p value
No—no. (%)	11 (92)	48 (84)	
Yes—no. (%)	1 (8)	9 (16)	0.068

CR complete remission, *uCR* unconfirmed complete remission, *PR* partial remission, *SD* stable disease, *PD* progressive disease

Furthermore, we did not analyze the cholesterol serum levels of our patients, but the recently published Japanese study showed no differences in the clinical outcome of patients with low levels of serum cholesterol [7].

In summary, we observed that patients taking statins did not do worse than patients not taking statins. Based on these data, we currently do not recommend our patients to stop statin medication during R-CHOP therapy. To further evaluate the prognostic value of statins in lymphoma patients and their mechanisms of action, more translational research is warranted.

Authorship and disclosures PS, HH, FS-L, and CR designed the study, collected, and analyzed the data and wrote the manuscript. SRH performed the statistical analysis, NGS performed the imaging analysis. RDS, UP, AM, AM, MZ, and AK participated in the patients' care and the data analysis.

All authors were involved in the revision process and approved the final manuscript. No conflicts of interest are present.

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